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CASE REPORT

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Tibial lenghtening through callus distraction in a patient with Schmid-type metaphyseal chondrodysplasia with a novel COL10A1-mutation

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Abstract

We report on a patient with Schmid-type metaphyseal chondrodysplasia (MCDS) carrying a novel COL10A1 mutation who underwent bilateral tibial lengthening at the age of 16.5 years using the technique described by Ilizarov. The disease-causing mutation Phe554Leu (g. 1660 T>C) represents the most amino terminal mutation within the NC1-domain of collagen type X described in MCDS so far. Failure of consolidation of the anterior distraction callus required secondary conversion to intramedullary nailing 344 days after primary surgery. Length gained was 5 cm (17.2% of tibial length), and healing index was 160 days/cm (46.5 days/percentage). This is the first case of callus distraction reported in a patient carrying a defined collagen X missense mutation. The associated defect in endochondral ossification may represent a central factor leading to the failure of callus consolidation.

Key words: *NC1-domain, X missense mutation, endochondral ossification, Schmid-type metaphyseal chondrodysplasia*

Introduction

Schmid-type metaphyseal chondrodysplasia (MCDS) is the most common type of metaphyseal chondrodysplasia and is caused by a mutation of the *COL10A1* gene (located at chromosome 6q21-q22) [1,2]. As collagen type X is normally expressed in the hypertrophic zone of the growth plate adjacent to the calcifying cartilage, a mutation of *COL10A1* interferes with endochondral ossification. Typical clinical features apart from disproportionate short stature include some lumbar hyperlordosis and waddling gait as well as remarkable bowlegs and coxa vara [3,4].

Callus distraction is an effective and elegant technique for surgical limb lengthening as surgeons "can create a growth plate anywhere in the bone" - as *Ilizarov* put it [5]. Since the underlying principle depends on the creation of an artificial growth plate, application in patients with inherited disorders of growth plate function might be problematic. It has been shown that callus distraction can be successfully performed in achondroplasia or hypochondroplasia - two conditions caused by mutations of fibroblast growth factor receptor 3 (FGFR3) [6-8]. For other types of skeletal dysplasia affecting endochondral ossification only few reports on successful callus distraction exist.

We report on the problems arising during callus distraction in a 16 year-old female MCDS patient carrying a missense mutation within the NC1-domain of collagen type X.

Case report

The patient presented in our institution at the age of 16 years suffering from the psychological consequences of both her short stature and bowlegs. She was born to non-consanguineous parents, both immigrants from Turkey. The patient's family history was inconspicuous as to the maternal side. The patient's father presented with features such as disproportionate short stature with short legs and bowlegs. His standing height was 164 cm (1,45 SD compared to average male Turkish population [9], and his sitting height was 92 cm. At the age of 4.7 years, the patient had undergone valgus intertrochanteric osteotomy at an outside hospital due to progressing coxa vara, the osseous healing process had been normal.

The patient's body height at the age of 16.2 years was 140 cm (19 cm below 3rd centile, Figure 1). Sitting height was not reduced (81 cm at the age of 16.2 years) indicating disproportionate short stature. Clinical findings included hyperlordosis, and a 16° varus deformity of both legs (Figure 2).

A mutation screening within the *COL10A1* gene of genomic DNA was performed by means of PCR amplification and consecutive sequencing in the patient and in both of her parents. An identical missense mutation (g. 1660 T>C) resulting in the replacement of phenylalanine by leucine at position 554 (Phe554Leu) was found in both her father's sample and her own. Her mother did not carry the mutation.

To comply with the patients request for lengthening we decided to perform axis correction and tibial lengthening with callus distraction using the technique described by Ilizarov. At the age of 16.5 years we performed simultaneous procedure on both tibiae. The fibula was dissected within the distal third and the distal fragment of the fibula was fixed to the tibia by means of a transfixation wire. Tibial osteotomy was performed within the proximal third of the tibial diaphysis through an anterior approach. After acute correction of the axis deformity (16° varus) and rotational deformity (20° internal rotation) the connecting rods and the distractors were placed.

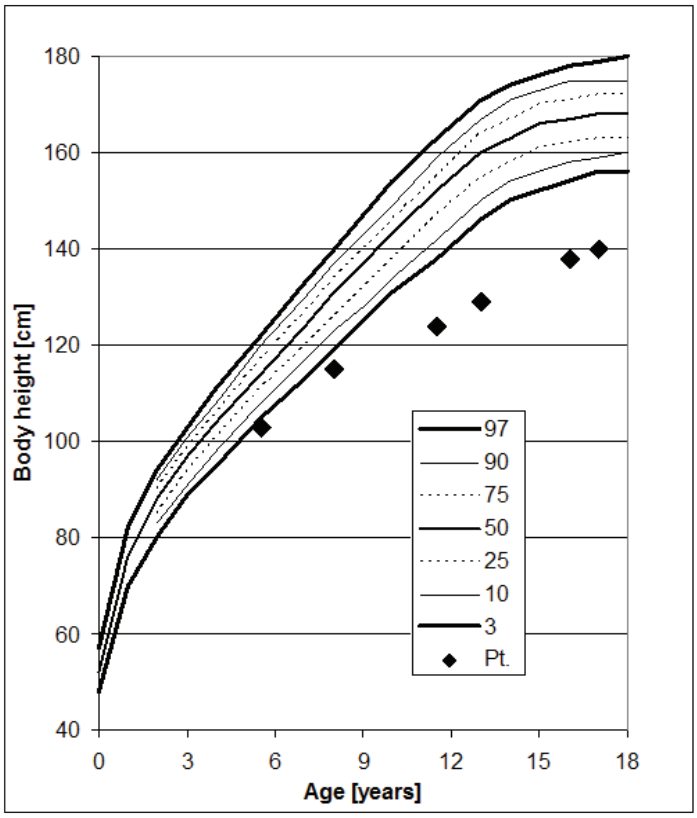

Figure 1. *Growth chart of the patient (Pt.)*

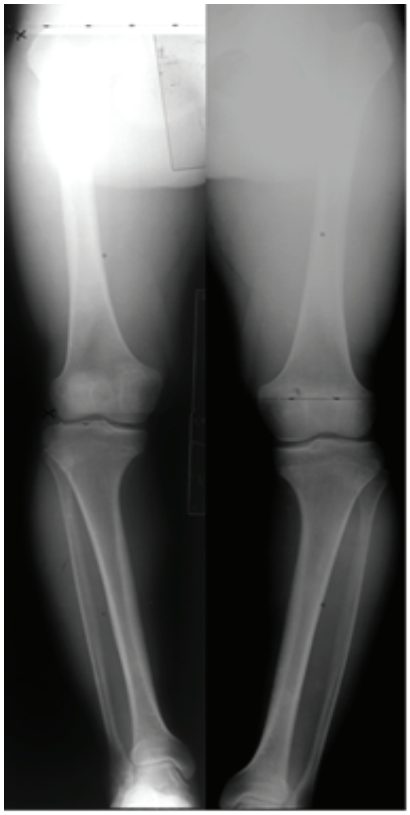

Figure 2. *Persisting bowlegs at the age of 16 years.*

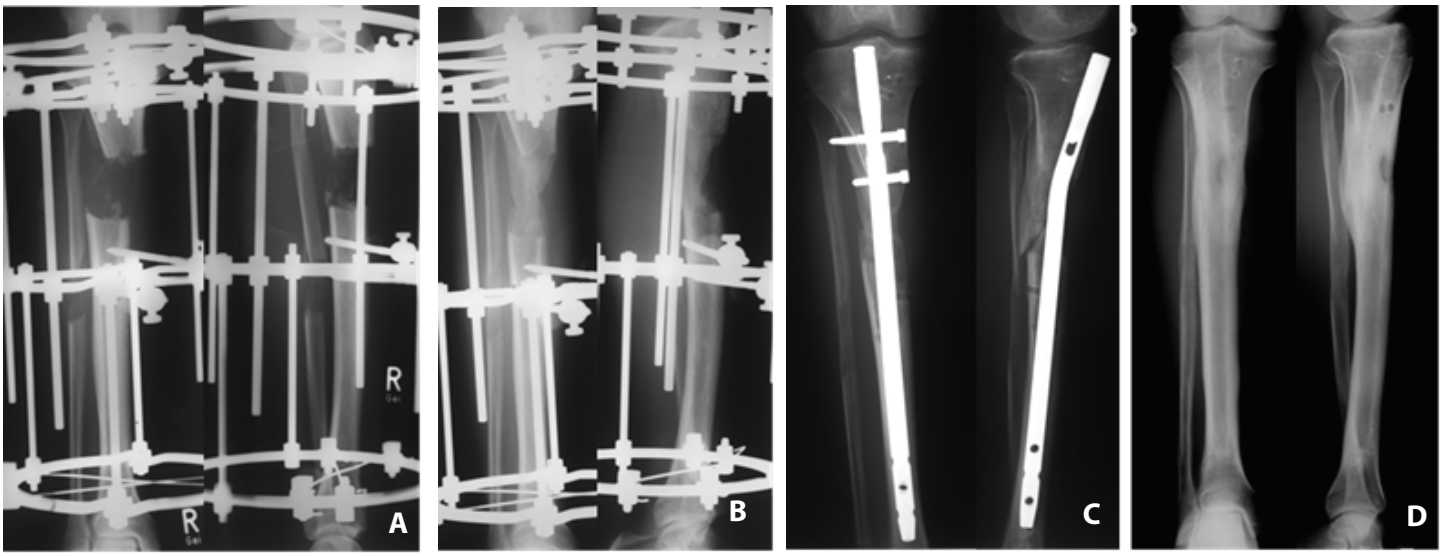

Figure 4. *A) Right tibia a.p. and lateral on the 44th day, B) on the 181st postoperative day, C) after intradmedullary nailing on the 344th day and D) after hardware removal on the 853rd day.*

On the first postoperative day compartment syndrome was suspected bilaterally, and prophylactic fasciotomy was performed immediately. However, the diagnosis could not be confirmed intraoperatively. Postoperatively full-weight bearing was permitted; distraction began seven days after surgery at 1 mm per day. Neither pin infection nor joint contractures were seen during distraction phase. On the 56th postoperative day the planned distraction length of 5 cm or 17.2% of tibial length was reached. Serial X-rays taken during consolidation phase initially showed substantial callus calcification which was, however, restricted to the posterior half of the distraction gap (Figure 3A and 3B). When approximately one year after surgery callus formation had not yet been observed in the anterior part of the distraction gap, the external fixator was removed and replaced by a reamed tibial nail on the 344th postoperative day (Figure 3C). Six month after intramedullary nailing consolidation of the anterior callus was seen, fifteen months after intramedullary nailing 800 days after the beginning of callus distraction – hardware was finally removed (Figure 3D).

Full range of motion of all adjacent joints as well as tibial length gained and correction of axis could be maintained. Overall distraction length was 5 cm in both tibiae or 17.2 % of tibial length. The external fixation index and healing index (external fixation time respectively healing time/length gained) were 68.8 days/cm (20 days/percentage) and 160 days/cm (46.5 days/percentage).

Discussion

The case presented depicts a protracted clinical course of surgical limb lengthening by callus distraction in a patient with SMCD. Due to failure of consolidation of the anterior distraction callus requiring secondary conversion to intramedullary nailing the healing index we found was extremely high (160 days/cm) compared to data in literature (8-110 days/cm) [6,10].

Delayed ossification of the anterior distraction callus is not unusual when callus distraction is performed in otherwise healthy patients. It is generally attributed to a mild tibial recurvatum caused by tension of the gastrocnemius muscle, which results in a decrease in pressure within the anterior distraction callus when compared to its posterior part. In the case presented, however, the delay in ossification of the anterior distraction callus was far beyond any we had experienced in otherwise healthy patients. Thus, it might be suggested that the delay in bone calcification was caused by the underlying molecular defect of MCDS as it affects the process of endochondral ossification.

So far, only Noonan et al. [11], reported on 18 patients with metaphyseal chondrodysplasia who underwent successful callus distraction. With regard to complication rate, length gained and healing index their results did not differ significantly from those of patients with other etiologies. The authors, however, did not specify which type(s) of metaphyseal chondrodysplasia they dealt with, nor did they perform a mutation analysis. Therefore, it is uncertain whether they really treated a patient with MCDS carrying a mutation of collagen type X.

Collagen X is a homotrimeric molecule which consists of three identical α1(X)-chains. Each α1(X)-chain is formed of one helical collagenous domain and two globular domains (NC1-domain and NC2-domain). The NC1-domain plays a crucial part in the trimerization of α1(X)-chains as it acts as a "zipper" [1]. Over 30 different mutations of the *COL10A1*-gene have been linked to MCDS. Almost all of them are located in the NC1-domain which is probably due to its crucial role in the assembly of homotrimeric collagen X-molecules [1]. We found a new missense mutation g. 1660 T>C which results in the substitution of phenylalanine by leucine in position 554 located in the amino terminal portion of the NC1-domain. This position is quite unusual, since all mutations found in the NC1-domain so far are clustered in its carboxy terminal portion (between Tyr582 and Ser671) [1]. As clinical (short stature, short legs, bowlegs and coxa vara) and radiological (widening and irregular calcification of growth plates) findings in both father and daughter concur with all typical symptoms of MCDS [3,4], it may be safely assumed that the mutation F554L found is causing MCDS. Recently, studies on pathogenetic consequences of *COL10A1* mutations have implicated a gain-of-function effect causing endoplasmatic reticulum stress [12]. It has been shown that certain *COL10A1* mutations lead to altered chondrocyte differentiation and function [13,14]. Moreover, diminished expression of VEGF in hypertrophic chondrocytes impairing vascular invasion during endochondral ossification was reported [13]. Since vascular invasion is associated with the recruitment of osteo-/chondroclasts to degrade cartilaginous tissue and osteoblastic cells for bone formation a respective pathogenetic mechanism might also be involved in delayed ossification of a distraction callus.

In conclusion, limb lengthening through callus distraction in patients with MCDS should be critically discussed: Since endochondral ossification is impaired surgical limb lengthening might be associated with protracted healing. Further observations on distraction callus consolidation in patients carrying mutations of collagen type X may help to clarify whether delayed consolidation observed in our case can be mainly attributed to the primary molecular defect.

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